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APPENDIX A

Patent
Attorney's Docket No. 000951-089

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Joseph B. PHIPPS	)	Group Art Unit: 3734
	)	
Application No.: 08/463,904	)	Examiner: M. Bockelman
	)	
Filed: June 5, 1995	)	
	)	
For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL	)	

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Joseph Bradley Phipps, hereby declare that:

1. I am a citizen of the United States of America residing in Maple Grove, Minnesota.

2. I received my undergraduate degree in Materials Science from University of Utah and my doctorate in Materials Science from Northwestern University.

3. I have been employed by Alza Corporation since 1991 and my current title is Director of Research, E-Trans Technology and my responsibilities include performing research in materials science and electrotransport devices, particularly waveform parameters such as voltage, current and timing to enhance biocompatibility and drug flux.

4. I am the inventor of the above-identified patent application and the Declarant of the Declaration previously submitted in the present application. I have reviewed the Official Action dated April 2, 1998, and I am familiar with the prior art cited in the Action which includes two U.S. patents identifying me as a co-inventor.

5. The Examiner's statements in the Official Action misinterpret the teachings of the prior art and several of the points which I made in my previous Declaration and are technically incorrect concerning certain aspects. In particular, the Examiner questions why I did not address the one sentence statement found in one of my previous patents, namely U.S. Patent No. 5,125,894, and instead discussed the Padmanabhan article that is referenced in the parent. The simple answer to this question is that the statement in the '894 patent is based on the Padmanabhan article and rather than discuss the statement through the '894 patent, I believed that it was proper to discuss the source of the statement and explain the reasons why the article did not teach my invention.

Nonetheless, to address the Examiner's concern that I did not expressly discuss the '894 patent, I note that the Examiner correctly points out that the '894 patent discloses the concept that a threshold concentration exists, below which the flux becomes concentration dependent, and that this threshold will likely be dependent on the physical/chemical properties of the transported species and tissues. This statement requires no unique knowledge of drug transport and is an entirely obvious concept. That is, since drug flux was known to be independent of drug concentration over some concentration range (e.g., as stated in the Padmanabhan article), and since drug flux is obviously zero at zero

concentration, then to conclude in the '894 patent that a "threshold value" exists is an obvious concept requiring no unique knowledge about the mechanism of drug transport through the tissue. In addition, the statement in the '894 patent that this threshold value is likely dependent on the physical/chemical properties of the drug species and tissues is also an obvious general principle which is devoid of mechanistic or drug-specific knowledge.

It is clear that the '894 patent is completely silent on the magnitude of the threshold value and on what physical/chemical properties of the drug molecule or tissues might influence the threshold value. Instead the '894 patent cites the Padmanabhan article as supportive of the general principles presented. In the Padmanabhan article, the range of concentration over which the flux of hydromorphone is constant is shown to be very broad and to extend to a very low value of less than 1 mM (ie, less than about 0.5 mg/ml hydromorphone). The Padmanabhan article notes that the transport number of hydromorphone in solution was greater than the transport number through the skin, and concludes:

> Therefore, the hydromorphone concentration at the skin will be greater than the bulk solution value during iontophoresis. This phenomenon may be responsible for the **lack of dependence of the transdermal delivery rate on the bulk solution concentration.** (emphasis added at page 130)

In other words, due to the mobility of the ions in the solution, the rate limiting feature is the transport through the skin and not the concentration in the donor reservoir. It would be understood by those in the art that this phenomenon is not limited to hydromorphone and would be applicable to other drugs. Accordingly, from this statement

and others in the article, it is clear that the concern for the effect of a threshold value on system performance would be diminished, not enhanced by the Padmanabhan article, which represents the depth of understanding at the time of the present invention. In contrast, my discovery that fentanyl and sufentanil have high threshold concentrations could not have been predicted from any statement made in the Padmanabhan article or, for that matter, in the '894 patent. Further proving this point is the fact that Table 2 in column 37 of the '894 patent shows that even at 10 millimolar concentration, hydromorphone exhibits a delivery rate that is comparable to much higher concentrations which supports the statement in the Padmanabhan article that I referred to in my previous Declaration that the delivery of hydromorphone was not influenced by donor solution concentration until the concentration dropped to about one millimolar which is well below the level of my invention.

While secondary to my primary disagreement with the Examiner on what is obvious and what is not, the Examiner has seemingly failed to appreciate the role of extraneous ions on the threshold concentration concept. This misinterpretation is understandable since many researchers in this field to this day fail to grasp the finer elements of the competing ion effect.

The Examiner incorrectly asserts that; (a) the presence of extraneous ions like Na^+ and K^+ in a formulation diminishes the relevance of the Kasting model cited in my previous Declaration; and, (b) that the reason that a higher threshold is observed for some drugs may be due to the extraneous ion concentrations in the formulation employed.

In making these assertions, the Examiner is assuming that the extraneous ions, if present at the beginning of treatment are still present at the end of treatment. In fact, because small excipient ions (like Na^+ and K^+) are much more mobile in the solution and skin than the fentanyl ions and are typically present in an amount less than the amount of the drug ions, they are substantially depleted during the first part of treatment. Therefore the Kasting model is an important and fully appropriate consideration of the state of the art at the time of my invention. Contrary to the Examiner's assertions, the Kasting model teaches away from my invention, even when extraneous ions are initially present, since it predicts in theory that no threshold in concentration should exist, that is, that the flux of drug at constant current should remain essentially constant until the last molecule is delivered.

3 no proof

The Padmanabhan article largely confirms the theory by proving that the flux of hydromorphone is independent of concentration over a broad range extending to a small drug concentration of less than 1 mM. It is therefore not proper for the Examiner to discount the importance of the Kasting model and the Padmanabhan teachings in defining the state of the art at the time of my invention.

With respect to the rejection based on Haak et al, U.S. Patent No. 5,203,768, I could not find sufficient information concerning the examples to determine the concentration of fentanyl at the end of use. However, Haak et al does not diminish the value of my discovery. The invention does not seek to define the initial concentration of the drug in the donor reservoir, but rather to limit the allowable magnitude of the final

concentration after the system has completed its period of operation. The patent clearly provides insufficient information about the formulation, system geometry, operating current, and maximum duration of operation to estimate the concentration of fentanyl in the formulation after use of the system. More importantly, Haak et al is completely silent on the issue addressed by my invention, namely, the maintenance of drug flux throughout the treatment period intended for the system. This important consideration for developing an optimal system is clearly unappreciated by Haak et al.

The Examiner's combination of Haak et al with the '894 patent would also not result in my invention. As noted above, a proper understanding of what the '894 patent teaches would lead those in the art to using a low concentration of fentanyl salt in view of the teaching that steady state delivery can be obtained at very low concentrations and in light of the potency of fentanyl. It is entirely unexpected that I have found that a very high concentration of fentanyl salt is necessary in order to obtain the iontophoretic flux defined in the claims.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 3, 1998
Date

Joseph B. Phipps